Neurocognitive Effects of Radiation Therapy in Pediatric Brain Tumor Survivors

Samantha E. Smith

Thesis Completed in partial fulfillment
of the requirements of the
Honors Program in Psychological Sciences

Under the Direction of Prof. Bruce E. Compas

Vanderbilt University

29 March 2012

Approved _____

Date _____

Dr. Bruce Compas

Thesis Mentor, Stress & Coping Lab

Kristen Robinson

Doctoral Student, Stress & Coping Lab

Dr. Megan Saylor

Psychology Research with Honors Program Director

Thesis Committee Members

ABSTRACT

This study characterizes the neurocognitive late effects of treatment in pediatric brain tumor survivors by examining patterns of executive function, coping, emotional outcomes, and brain activation. We examined associations among these variables and their relationship to prefrontal cortex activation in 20 children and adolescents ages 8 to 16-years old who completed treatment for a pediatric brain tumor with 20 healthy controls matched on age and sex. We found partial support for our hypothesis that survivors perform worse than healthy controls on these domains and that activation patterns during executive function tasks differ. No causal relationship among executive function, coping, and emotional outcome variables was found. Findings suggest that neurocognitive deficits in survivors may be associated with impairment in prefrontal cortex integrity.

Pediatric brain tumors are a significant threat to the health of thousands of children in the U.S. today. As the most common solid tumor diagnosis in children, pediatric brain tumors constitute 20-25% of all childhood malignancies (Panigraphy & Bluml, 2009) and are the second leading cause of death by disease in children (Central Brain Tumor Registry of the United States; CBTRUS, 2011). CNS tumor diagnoses occur at a rate of 4.3 cases per 100,000 children, making them the second leading pediatric cancer diagnosis (Nathan, Patel, Dilley, Goldsby, Harvey, Jacobsen et al., 2007; Gottardo & Gajjar, 2008). Brain tumor diagnoses are heterogeneous; over 100 subtypes of pediatric brain tumors exist, with the most common being medulloblastomas, pilocytic astrocytomas, and ependyomas (Panigraphy & Bluml, 2009). Despite the prevalence of brain tumor diagnoses among children, 5-year survival rates have increased to 74% in children diagnosed below 20 years of age (Nathan et al., 2010). Improvement in survival is largely due to modifications in treatment protocols, with many patients receiving a combination of surgery, radiation, and chemotherapy (Gotardo & Gajjar, 2008). As survival rates for pediatric brain tumor patients continue to rise, increasing focus has turned to improving the long-term quality life for these children.

There are costs associated with effective treatment, as many survivors experience limitations in physical performance, endocrine function, and cardiac impairment in the years following recovery (Ness & Gurney, 2007). Even more, for many pediatric brain tumor survivors, the late effects of treatment extend to impairments in neurocognition and increases in emotional problems. Neurocognitive effects are pervasive, with studies reporting 40-100% of survivors experiencing some form of cognitive deficit following treatment (Glauser & Packer, 1991). Affected cognitive domains include overall intelligence,

executive function, memory, and academic achievement (Glauser & Packer, 1991, Mulhern & Butler, 2004). Although the direct cause remains unclear, deficits likely occur as a result of tumor size, location, surgery, radiation, and chemotherapy (Glauser & Packer, 1991). Further, some survivors also experience increased levels of emotional problems as compared to their healthy siblings, with higher measures of global distress and depression (Zebrack & Chesler, 2001).

To address some of these important concerns regarding survivors of childhood brain tumors, the current study had three goals. First, this study was designed to further characterize the nature of neurocognitive deficits and emotional problems in pediatric brain tumor survivors as compared to their healthy control peers. Secondly, we sought to identify the relationships between neurocognitive performance, coping skills, and emotional problems. And finally, this study investigated the relationship between brain activation and measures of neurocognitive functioning between these two groups.

Brain tumor treatment is somewhat unique from other common pediatric cancers in that it often involves cranial (whole brain) radiation therapy. Children respond differently to brain tumor treatment than their adult counterparts, and their treatment more commonly involves craniospinal irradiation (Merchant, Pollock, & Loeffler, 2010). Pediatric patients treated with whole brain or craniospinal radiation therapy have experienced significant neurocognitive effects in memory and executive function in years following treatment (Nathan et al., 2007).

The neurocognitive effects on survivors can be severe. As a whole, many survivors perform a full standard deviation below norms on cognitive tasks (Robinson et al., 2010). Specifically, children treated for brain tumors exhibit pervasive and substantial deficits in

broad and specific neurocognitive domains including cognitive function, academic achievement, attention, psychomotor and visual-spatial skills, verbal memory, and language (Robinson et al., 2010). Longitudinal analyses have shown that intelligence scores in survivors decline over time, with the most significant drop in the first few years following treatment (Speigler, Bouffet, Greenberg, Rutka, & Mabbott, 2004). Long-term deficits have been observed in visual-motor integration, visual memory, verbal fluency, and executive function (Spiegler, Bouffet, Greenberg, Rutka, and Mabbott, 2004). Even so, the statistical power in prospective studies has been limited due to small sample size and poor design, and the true pattern of recovery is still unclear.

The factors underlying differences in neurocognitive function are largely unknown, although associations with tumor type, radiation therapy, and age at diagnosis have been documented. Some reports have found greater deficits in task efficiency and organization in pediatric survivors of medulloblastomas and PNET tumors as compared to survivors of other tumor types (Nathan et al. 2007). Even so, tumors themselves do not appear to be the primary cause of cognitive deficits, as children receiving cranial radiation treatment are more likely to have neurocognitive and psychosocial deficits that require remedial intervention (Copeland, deMoor, Moore, & Ater, 1999). Increasing attention has been given to the role of radiation therapy, as it has been reported to increase risk of long-term neurocognitive, endocrine, and neurological effects (Merchant et al., 2010). In cases where radiation is administered in a dose greater than 30 Gy, deficits in memory have been reported in temporal lobe radiation among brain tumor survivors (Nathan et al. 2007).

Involvement of the pre-frontal cortex (PFC) is of particular interest. Damage to the prefrontal cortex has been correlated with impairment in executive functioning, a domain

consistently reported as being hard hit by radiation (Alvarez & Emory, 2006). However, this is not a one-to-one relationship, suggesting the involvement of other neural pathways or regions (Alvarez & Emory, 2006). Damage to white matter between the cerebellar pathway and frontal region has been associated with deficits in processing speed, suggesting a dependency between executive function and white matter integrity (Nathan et al. 2007). Despite these suggestions, the heterogeneity of reported effects suggests that moderating variables exist, making some children differentially susceptible to long-term effects than others (Robinson et al., 2010). Most likely, outcome is determined by the combination of treatment type, medical and treatment complications, and tumor type (Stargatt, Rosenfield, Maixner, & Ashley, 2007).

Emotional problems are also common in many survivors of pediatric brain tumors, although evidence of these symptoms vary among studies (Fuemmeler, Elkin, Van Pelt, Carpentier, & Parkhurst, 2005). For example, in a study by Carpentieri et al., (1993) brain tumor survivors exhibited significant elevations on Behavior Problems scales of the Child Behavior Checklist relative to non-clinical norms. Even so, 50% of children in this group did not experience these effects (Carpentieri, 1993), suggesting that emotional outcomes may affect a subgroup of survivors. In general, brain tumors survivors exhibit more deficits in internalizing (e.g., anxiety, depression) than externalizing (e.g., aggression) behavior (Carey, Barakat, Foley, Gyato, & Phillips, 2001). Most common among these deficits are symptoms of anxiety and depression (Fuemmeler et al., 2005). Survivors have been shown to be 1.5 times more likely to exhibit symptoms of depression and anxiety than their healthy peers, and risk factors have been linked to cranial radiation and intrathecal methotrexate treatment (Schultz et al. 2007). Further, chemotherapy treatment has been

linked to more internalizing and externalizing behavior problems, especially in areas of social withdrawal and anxious depressive symptoms (Holmquist, & Scott, 2002). Despite these findings, a study by Mabbott et. al (2005) found that emotional outcomes in pediatric brain tumor survivors were not related to radiation dose, extent of surgery, or treatment with chemotherapy. Although evidence of poorer emotional outcomes among pediatric brain tumor survivors exists, the direct cause of these symptoms and their relation to other late effects remains unclear.

Deficits in neurocognitive functioning among pediatric brain tumor survivors may be associated with these children's ability to cope with stress, as these processes are associated with the higher level thinking of the prefrontal cortex. For example, in a study of Acute Lymphocytic Leukemia (ALL) patients, performance on executive function measures was linked to the ability to cope with stress and with emotional and behavioral problems in these children (Campbell, Scaduto, Van slyke, Niarhos, Whitlock, & Compas, 2009). Impairment in executive functioning in these children was associated with increased coping and emotional issues, although this correlation is not seen in all patients (Campbell et al., 2009). Similarly, executive function has been shown to play an indirect role in the ability to control anxiety and depression through coping in youth with chronic abdominal pain (Hocking, Barnes, Shaw, madan-Swain, & Saeed, 2011). In these children, coping was mediated by skills in selective attention, suggesting executive function may be a key factor in differential emotional outcomes among these children (Hocking et al., 2011). The role of coping in the emotional adjustment of pediatric brain tumor survivors is still unknown, but is suspected to demonstrate a similar pattern.

Voluntary coping responses are of particular interest in this study and has been defined as the "conscious, volitional efforts to regulate emotion, cognition, behavior, physiology, and the environment in response to stressful events or circumstances" (Compas et al., 2001). Coping can be subdivided into engagement behavior, in which the person orients oneself toward the stressor, and disengagement behavior, in which the person orients oneself away from the stressor (Compas et al., 2001). Engagement coping can be further divided into primary and secondary control measures. Primary control coping seeks to respond to the stressor through problem solving, emotional modulation, and emotional expression. Secondary control coping seeks to regulate one's reactions to the stressor through positive thinking, cognitive restructuring, acceptance, and distraction. Disengagement coping constitutes behaviors of avoidance, denial, and wishful thinking. Greater primary and secondary control coping is associated with lower emotional and behavioral problems in children and adolescents, whereas disengagement is associated with higher levels in these measures (Compas et al., 2001).

Although the cognitive deficits in pediatric brain tumor survivors are clear, the underlying brain activation must be understood in order to understand the neural mechanisms linking cognitive performance and emotional adjustment. Functional magnetic resonance imaging (fMRI) has consistently shown activation in the PFC in tasks of executive functioning (Collette, Hogge, Salmon, & Van der Linden, 2006) and these activations differ between brain compromised individuals and healthy controls (McAllister et al., 1999). In a study of adolescents with fetal alcohol syndrome, prefrontal activation increased in response to verbal working memory and inhibition demands, suggesting that frontal structures are taxed more for individuals with damaged cortex (Spadoni, Bazinet,

Fryer, Tapert, Mattson & Riley, 2009). In a study of multiple sclerosis patients, fMRI was used to identify neural mechanisms underlying executive function deficits (Sweet, Rao, Primeau, Durgerian, & Cohen, 2006). Scanning during working memory tasks allowed demands on the prefrontal cortex to be seen. Activation, as measured by blood oxygenated level dependency (BOLD), suggested that individuals with neural impairment recruited more blood than their healthy peers during difficult working memory tasks (Sweet et al., 2006). As pediatric brain tumor survivors exhibit deficits in executive function, it is anticipated that they will exhibit a similar increase in activation during working memory demands as compared to healthy peers.

The focus of the current study is first to further characterize neurocognitive functioning, emotional adjustment, and coping behavior in survivors of pediatric brain tumors as they compare to healthy control peers. It was hypothesized that survivors will perform worse on measures of neurocognitive functioning, exhibit poorer emotional adjustment, increased disengagement coping, and decreased primary and secondary control coping. Secondly, this study was designed to better understand the relationship among these variables. It was hypothesized that the association between poorer EF and poorer emotional outcomes is explained by differences in coping. And lastly, to determine brain activation patterns in these children during demands on the pre-frontal cortex. It was hypothesized that during difficult working memory tasks, survivors will perform with less accuracy and will show higher activation in the pre-frontal cortex than healthy controls.

METHODS

Participants

Participants included 20 pediatric brain tumor survivors (12 girls) and 20 healthy control children (9 girls). Survivors were recruited from the Childhood Cancer

Survivorship Clinic in the Department of Pediatric Hematology and Oncology, or the Department of Neurology, at Vanderbilt University Monroe Carrel Jr. Children's Hospital. Healthy control participants were recruited through the Vanderbilt University Kennedy Center Study Finder program and were matched on age and gender to brain tumor participants. Inclusion criteria for survivors included treatment for a malignant or nonmalignant brain neoplasm at Vanderbilt Children's Hospital, continuous first remission, completion of all PBT-related treatment, and English fluency. Exclusion criteria included history of pre-existing neurodevelopmental disorder prior to PBT diagnosis, history of low birth weight (<1500 grams), and history of secondary malignancies and relapses. Inclusion criteria for healthy controls included English fluency, history of cancer, history of central nervous system pathology requiring radiation or surgery, history of pre-existing neurodevelopmental disorder, and history of low birth weight (< 1500 grams). Participants recruited were between the ages of 8 and 18 years-old.

Eighteen survivors and 12 healthy controls self-identified as Caucasian, 1 survivor and 6 healthy controls identified as African American, 0 survivors and 1 healthy control identified as Latino, and 1 participant in each group identified as Asian or Pacific Islander. At the time of enrollment, brain tumor survivors were on average 12.15 years old (SD=2.72) and healthy controls were on average 12.0 years old (SD=2.98). Participants in both groups ranged in age from 8-16 years old. The Vanderbilt University Institutional Review Board approved all procedures of the study, and every parent and participant signed consent and assent documents prior to testing.

Demographic information for participants is shown in Table 1. Between group *t*-tests and chi-square analyses were conducted to assess whether group matching was

successful. Results indicated that brain tumor survivors and healthy controls were similar in terms of age at enrollment (t = 5.69, p = .68), gender (X^2 = .90, p = .34), race (X^2 = 5.77, p = .12), and yearly household income (X^2 = 1.06, p = .59). The difference in primary care giver between the groups was approaching significance (X^2 = 3.24, p = .072). The level of the primary caregiver's education significantly differed between the two groups (X^2 = 4.44, p = .04). Overall, these results suggest that survivors and healthy controls were adequately matched in terms of demographic characteristics.

Design

Study participation included three components: completion of questionnaire measures; a neurocognitive assessment battery completed with a trained graduate student; and a neuroimaging session including structural, functional, functional connectivity, and diffusion tensor imaging. Neurocognitive assessments included measures of overall functioning, memory, visual-spatial integration, and executive function. Parents and children completed several questionnaire measures assessing various domains functioning, including psychosocial, emotional, behavioral problems, executive functioning, and coping.

Procedure

Families of brain tumor survivors received a physician letter informing them of the study and providing a contact number to call in order to decline participation. Healthy controls responded to an advertisement through the Vanderbilt University Study Finder website. A phone screen interview was conducted with each interested family to determine eligibility and to schedule assessment sessions for qualified children. Questionnaires and consent/assent forms were mailed to each family's home and obtained in person during

study appointments. After a research assistant answered all questions regarding the study, parents and children competed their appointments.

Assessment sessions were divided into blocks, including the neurocognitive testing and the scanning session. Participants completed the assessments during either one full day or two half-day visits, according to their availability. A trained graduate student led cognitive assessment tests during lab visits. Participants and parents completed remaining questionnaires during the cognitive assessment session.

Imaging was completed using a 3 Tesla MR scanner (Philips Medical Systems, The Netherlands) dedicated to research. The imaging protocol lasted 60-70 minutes and provided measures of brain tissue volume, function, and microstructure. The scanning session began by introducing parents and children to the mock scanner, a non-functioning replica of the MRI used in testing. Children were encouraged to enter the scanner to become comfortable with the enclosed space. Children were also shown the headset and the response pad that would be attached to each child's dominant hand during the scan. Children were taught how each of the computerized tasks that would appear overhead during the scan would run.

After all remaining questions were answered, children were taken back to the scanning room where they were placed in the scanner by a certified technician and trained study personnel. In addition to the response pad, participants wore a pulse oximeter on their non-dominant index finger to record heartbeat and a respiration belt over their diaphragm to record respiration rate. Protocols were run via computer in an adjacent room, and task stimuli appeared via a rear projector on a screen mounted in the MRI. Participants responded to questions by using buttons on the response pad. Reciprocal

communication between the research team and the participant was possible throughout the scan through the use of a microphone and headphones.

Measures

Questionnaires. During the assessment session families completed questionnaires assessing multiple domains of psychological functioning. The Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000) was used to measure children's self-control and problem-solving skills through eight aspects of executive functioning. The BRIEF Working Memory Scale was used in these analyses. The child report version of the Response to Stress Questionnaire (RSQ; Connor-Smith et al., 2000) was used to measures coping and involuntary stress response in children. Here, measures of primary, secondary, and disengagement coping were assessed. The Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001) is a parent-report questionnaire used to assess behavioral and emotional problems in children. Analyses in the current study focused on internalizing behavior through measures of anxious/depressive symptoms, and withdrawn/depressive behavior. Parallel measures were assessed through the Youth Self-Report (YSR; Achenbach & Rescorla, 2001), a child self-report questionnaire.

Neurocognitive Assessment. At their assessment session, children completed a brief neurocognitive testing battery. Among other measures, children completed 8 subtests of the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV; Wechsler, 2003) to measure overall cognitive functioning, including general verbal and nonverbal intelligence, working memory and processing speed. In these analyses, participants' WMI was examined. The Working Memory Index (WMI) is composed of the Digit Span and Letter-Number Sequencing subtests. The Wechsler intelligence scales have demonstrated

excellent internal consistency and test-retest reliability, as well as established convergent and discriminant validity.

Functional Neuroimaging. During their first functional scan, participants completed the N-back task, which is designed to assess working memory. A letter version of the visual N-back task (Barch, Sheline, Csernansky, & Snyder, 2003) has been developed, and involves sequences of uppercase consonants. In the 0-back condition, participants were instructed to respond to a single target (i.e., V). In the 1-back condition, participants were instructed to respond only when the consonant was identical to the one preceding it (e.g., M, M). In the 2-back condition, participants responded only when the consonant was identical to the one presented two trials prior (e.g., M, T, M), and in the 3-back condition, participants responded when the consonant was identical to the one presented three trials prior (e.g., M, T, F, M). Each condition was presented three times in order of increasing difficulty, for a total of 12 blocks. Each block contained 15 consonants, and 3 of these consonants required a response. This task has been used effectively with children in this age group with no adverse effects (Robinson, Livesay, et al., 2010). N-back task performance data were extracted using ePrime software (Psychology Software Tools Inc., Pittsburgh, PA). Accuracy, reaction time, number of omissions, and number of false positive responses were calculated for each participant at each level of N-back difficulty. Overall accuracy and reaction time total scores across N back difficulty level were also calculated.

Data Analyses

fMRI Data Preparation. All functional data were analyzed using Brain Voyager QX software (Brain Innovation B. V., Maastrict). For each participant, functional images from the participants' N-back run were corrected for 3D motion. Motion correction results were

assessed to ensure that all data fell within movement criteria (>3mm displacement, 3° rotation). For participants whose movement exceeded the established criterion for fewer than 1/3 of any given condition of the N-back, this data was corrected an the dynamic scans corresponding to the time points of excessive motion were removed.

The functional data for each participant was aligned to the participant's high-resolution 3D anatomic dataset. Each participant's activation map was normalized to a common reference space (Talairach), using registration techniques. For the current analyses, a cluster threshold of 3 functional voxels was established for examining between group interactions and main effect of group, a cluster threshold of 8 functional voxels was established for examining the main effect of N-back level, and a cluster threshold of 6 functional voxels was established for examining specific N-back level contrasts between groups. Each of these cluster thresholds maintained a significance criterion of $p < .01$. Significantly activated clusters that met this criterion were considered further. Composite *t*-values were calculated to measure the degree of activation in each cluster for examination of specific N-back level contrasts.

Hypotheses

Study hypotheses were analyzed as follows:

Hypothesis 1. Pediatric brain tumor survivors will perform more poorly than healthy control peers on measures of executive function, coping, and internalizing measures (anxiety/depression and withdrawn/depressed).

Hypothesis 2. The relationship between deficits in executive functioning and increased internalizing behavior will be explained by problems in coping skills.

Hypothesis 3: Pediatric brain tumors survivors will perform more poorly than healthy controls in working memory tasks. As demands on the pre-frontal increase, brain activation in survivors will be greater than that seen in healthy controls.

RESULTS

Hypothesis 1: Group comparisons in neurocognitive functioning, coping, and emotional outcomes.

Between group analyses. Mean scores and standard deviations for each EF, coping, and emotional/behavioral measure, as well as the results of the t-tests comparing brain tumor survivors and healthy controls based on *T* scores, are reported in Table 2. Almost all mean executive function measures (BRIEF and WISC-IV) and Emotional/Behavioral Outcome measures (YSR and CBCL) fell within one standard deviation of the normative means. Exceptions were in measures of BRIEF Working Memory Scale and CBCL Withdrawn/Depressed for brain tumor survivors, which both fell within two standard deviations of the normative mean.

Comparisons between brain tumor survivors and healthy controls were made using independent sample *t*-tests (Table 2). On both measures of executive function, there were significant between-group differences in measures of working memory (BRIEF, $t = 2.177$, $p = .04$; WISC, $t = -2.80$, $p = .01$). When compared with healthy controls, BT scores fell significantly lower on the WISC-IV WMI and significantly higher on the BRIEF WMS (indicating higher problems in working memory). There were no significant between-group differences on three measures of Emotional/Behavioral outcomes; however, BT survivors demonstrated significantly higher measures of Withdrawn/Depressed symptoms on the CBCL. No significant between-group differences were detected for RSQ measures of coping.

Correlations among EF, Coping, and Emotional/Behavioral Outcomes. Correlations among measures of EF, coping, and emotional/behavioral outcomes were expected to be strong within both groups and are displayed in Table 3. As seen from the results of Table 3, group significantly correlated ($p < .05$) with both EF measures and with CBCL Withdrawn/Depressed symptoms. Performance on the WMI significantly correlated with all three measures of coping. Higher scores on the WMI corresponded to higher scores on primary control coping and disengagement behavior and lower scores on measures of secondary control coping. As expected, secondary control coping was negatively correlated with disengagement coping and YSR anxious/depressed symptoms. Disengagement coping was positively correlated with YSR measures of anxious/depressed and withdrawn/depressed symptoms. Both of the emotional outcome ratings were positively correlated with one another within both the YSR and CBCL.

Hypothesis 2: Regression analyses predicting CBCL Withdrawn/Depressed and Secondary Control Coping as dependent variables

Linear regression analyses were conducted to predict Withdrawn/Depressed symptoms on the CBCL and measures of Secondary Control Coping on the RSQ. Variables of group, WISC-IV WMI, and BOLD activation in Brodman's Area (BA) 32 were considered. BA 32 was chosen as a region of interest as it significantly differed between groups on the 3v0 task and is located in the pre-frontal cortex region.

The regression analysis with withdrawn/depressed symptoms as the dependent variable (Table 4) did not provide evidence that any of the variables uniquely accounted for differences between the groups on this measure. When considered alone, WMI negatively correlated with withdrawn/depressed symptoms; however, these effects were no longer

significant in the regression analyses in the presence of group. Although no variable uniquely accounted for differences between brain tumor and control groups, this model explained 40% of the variance between withdrawn/depressed scores on the CBCL in survivors and healthy controls ($R^2 = .40$). This suggests that all of the variables included in the regression analysis were related to children's withdrawn/depressed symptoms but these predictors accounted for shared rather than unique variance in these symptoms.

The regression analysis with secondary control coping as the dependent variable (Table 5) also did not provide evidence that any of the variables uniquely accounted for differences between the groups on the measures. The regression had an R^2 value of .21, which reflects a medium effect. Importantly, the WMI on the WISC-IV did remain a significant predictor of coping in the presence of group, however, this effect was no longer significant in the presence of other variables.

Hypothesis 3: Pre-frontal cortex activation and performance on 3v0 n-back task

In between group analyses, independent t-tests were performed between the two groups to determine differences in activation in BA 32 and in accuracy on different trials of the n-back between the two groups. Accuracy did not differ between survivors and healthy controls on 0, 1, and 2 back trials. However, there was a significant difference in activation when task difficulty was increased on the 3-back task, with brain tumor survivors performing less accurately than healthy controls ($p < .01$). BOLD activation was significantly lower for brain tumor survivors in BA32 on the 3-back task as compared to activation in healthy controls. A regression analyses with BOLD activation for BA 32 was performed. No measure uniquely accounted for differences in activation between these groups.

DISCUSSION

This study sought to further understand the neurocognitive late effects of treatment on pediatric brain tumor survivors through three primary hypotheses. First, based on previous literature (e.g., Fuemmeler et al., 2005; Mulhern & Butler, 2004; Robinson et al., 2010), it was hypothesized that survivors of pediatric brain tumors would perform poorer on measures of executive function, coping, and internalizing behavior than their healthy control peers. The data partially supported this hypothesis. On measures of executive function, brain tumor survivors performed significantly lower on both working memory measures than healthy controls. Brain tumor survivors scored significantly higher for symptoms of Withdrawn/Depressed behavior on the CBCL, but did not show differences on any other emotional outcome measures. Although these results may appear contrary to studies supporting lower emotional outcome in pediatric brain tumor survivors (Carey et al, 2001), current literature has not provided consistent findings in this domain (Fuemmeler et al., 2002). This pattern suggests that some children may be differentially susceptible to negative emotional outcomes after treatment, and risk factors for these late effects should be considered in future studies. Contrary to our hypothesis, no significant differences were found in coping between the two groups despite differences in executive function performance. Differences may have been present in a subgroup of survivors that were not detected by these analyses.

The WMI measure of executive functioning significantly correlated to all three measures of coping. This data supports previous findings linking executive functioning to coping skills in other cancer groups (Campbell et al., 2009), suggesting that this association can be expanded to brain tumor survivors. However, higher working memory scores

correlated to higher levels of disengagement coping and lower secondary control coping; this pattern would not be expected if executive function helps improves the ability to cope. Despite these findings, disengagement coping positively correlated with YSR measures of Anxious/Depressed symptoms, suggesting that reliance on avoidance and denial coping may be associated with depressive behavior. This pattern of results warrants attention and replication in future research.

Our second hypothesis predicted that the association between executive function and emotional outcomes would be explained by differences in coping between brain tumor survivors and healthy controls. Regression analyses failed to support our hypothesis. No single variable of EF, coping, group, or BOLD activation uniquely accounted for differences in CBCL Withdrawn/Depressed symptoms or secondary control coping. Even so, the relationship among these variables explained a large proportion of the variance in Withdrawn/Depressive symptoms when taken together.

Our third hypothesis predicted that that during difficult working memory tasks, survivors will perform with less accuracy and will show higher activation in the pre-frontal cortex than healthy controls. The data partially supported this hypothesis. During low-demand levels of the n-back task, survivors did not perform less accuracy than healthy controls. However, when task difficulty was at a maximum during the 3-back task, survivors performed significantly worse than healthy controls. These patterns suggest that deficits in neurocognition surface when demands on the pre-frontal cortex are high. Among regions of the pre-frontal cortex, activation in Brodman's Area 32 significantly differed between the groups during the 3-back trial. This region is located in the dorsal anterior cingulate region of the pre-frontal cortex (Vogt & Peters, 2004). Although other chronically

ill groups have shown increased activation during executive function demands as compared to controls (Sweet, 2006), brain tumor survivors recruited less blood to the PFC during heavy cognitive loads. This difference in activation between brain tumor groups and that reported by previous literature suggests that radiation may affect brain structure differently than other diseases and treatments. Further, no measure uniquely accounted for differences in activation between survivors and healthy controls. Group remained the greatest predictor in the presence of other variables. These results suggest that differences in activation may be due to another factor not considered in these analyses.

Overall, the findings provide further evidence that survivors of pediatric brain tumors suffer from impaired neurocognitive function as compared to their healthy peers. The study makes an important contribution to current literature through its investigation of the neural basis underlying these late effects. However, the current study has several limitations. First, the small sample size of 20 participants in each group limited the statistical power to detect small effects between groups and in correlations among variables. A larger sample size would allow finer detection of differences in neurocognition between these groups. In order to determine risk factors that make some survivors differentially susceptible to these late effects, factors such as tumor type, tumor extent, and treatment dosage should be examined in future research. The cross sectional structure of this study limited the ability to infer the direction of causal relationships between the variables that would only be possible through a longitudinal design. Despite these limitations, the results from this study give important insight to the neurological basis of neurocognitive deficits in brain tumor survivors. Reduction in pre-frontal cortex activation during demanding working memory tasks suggests that the pathway undermining these

processes has been disrupted in survivors. As the nature of these neurocognitive deficits continues to become clearer, future studies should focus on developing interventions to remit the late effects of treatment on pediatric brain tumor survivors.

REFERENCES

Alvarez, J. A., & Emory, E. (2006). Executive function and the frontal lobes: A meta-analytic review. *Neuropsychology Review, 16*, 17-42.

Achenbach, T. M., & Rescorla, L. A. (1991). *Manual for the Child Behavior Checklist/14-18 and 1991 profile.* Burlington: Department of Psychiatry, University of Vermont.

Barch, D. M., Sheline, Y. I., Csernansky, J. G., & Snyder, A. Z. (2003). Working memory and prefrontal cortex dysfunction: Specificity to schizophrenia compared with major depression. *Biological Psychiatry, 53*, 376-384.

Campbell, L. K., Scaduto, M., Van Slyke, D., Niarhos, F., Whitlock, J. A., & Compas, B. E. (2009). Executive function, coping, and behavior in survivors of childhood acute lymphocytic leukemia. *Journal of Pediatric Psychology, 34*, 317-327.

Carey, M. E., Barakat, L. P., Foley, B., Gyato, K., & Phillips, P. C. (2001). Neuropsychological functioning and social functioning of survivors of pediatric brain tumors: Evidence of nonverbal learning disability. *Child Neuropsychology, 7*, 265-272.

Carpentieri, S. C., Mulhern, R. K., Douglas, S., Hanna, S., & Fairclough, D. (1993). Behavioral resiliency among children surviving brain tumors: A longitudinal study. *Journal of Clinical Child Psychology, 22*, 236-246.

CBTRUS (2011). Statistical Report: Primary Brain Tumors in the United States, 2004-2007. Published by the Central Brain Tumor Registry of the United States.

Collette, F., Hogge, M., Salmon, E., & Van der Linden, M. (2006). Exploration of the

neural substrates of executive functioning by functional neuroimaging. *Neuroscience, 139*, 209- 221.

Compas, B. E., & Boyer, M. C. (2001). Coping and attention: Implications for child health and pediatric conditions. *Journal of Developmental and Behavioral Pediatrics, 22*, 323-333.

Copeland, D. R., deMoor, C., Moore, B. D., & Ater, J. L. (1999). Neurocognitive development of children after a cerebellar tumor in infancy: A longitudinal study.*Journal of Clinical Oncology, 17*, 3476-3486.

Fuemmeler, B. F., Elkin, T. D., & Mullins, L. L. (2002). Survivors of childhood brain tumors: Behavioral, emotional, and social adjustment. *Clinical Psychology Review, 22*, 547-585.

Glauser, T. A., & Packer, R. J. (1991). Cognitive deficits in long-term survivors of childhood brain tumors. *Child's Nervous System, 7*, 2-12.

Gottardo, N. G., & Gajjar, A. (2008). Chemotherapy for malignant brain tumors of childhood. *Journal of Child Neurology, 23*, 1149-1159.

Hocking, M. C., Barnes, M., Shaw, C., Lochman, J. E., Madan-Swain, A., & Saeed, S. (2011). Executive function and attention regulation as predictors of coping success in youth with functional abdominal pain. *Journal of Pediatric Psychology, 36*, 64-73.

Holmquist, L. A., & Scott, J. (2002). Treatment, age, and time-related predictors of behavioral outcome in pediatric brain tumor survivors. *Journal of Clinical Psychology in Medical Settings, 9*, 315-321.

Mabbott, D. J., Spiegler, B. J., Greenberg, M. L., Rutka, J. T., Hyder, D. J., & Bouffet, E.

(2005). Serial evaluation of academic and behavioral outcome after treatment with cranial radiation in childhood. *Journal of Clinical Oncology, 23*, 2256-2263.

McAllister, T. W., Saykin, A. J., Flashman, L. A., Sparling, M. B., Johnson, S. C., Guerin, S. J., … Yanofsky, N. (1999). Brain activation during working memory 1 month after mild traumatic brain injury: A functional MRI study. *Neurology, 53*,1300-1308.

Merchant, T. E., Pollack, I. F., & Loeffler, J. S. (2010). Brain tumors across the age spectrum: Biology, therapy, and late effects. *Seminars in Radiation Oncology, 20*, 58-66.

Mulhern, R. K., & Butler, R. W. (2004). Neurocognitive sequelae of childhood cancers and their treatment. *Pediatric Rehabilitation, 7*, 1-14.

Nathan, P. C., Patel, S. K., Dilley, K., Goldsby, R., Harvey, J., Jacobsen, C., et al. Armstrong, F. D. (2007). Guidelines for identification of, advocacy for, and interventions in neurocognitive problems in survivors of childhood cancer: A report from the Children's Oncology Group. *Archives of Pediatric and Adolescent Medicine, 161*, 798-806.

Ness, K. K., & Gurney, J. G. (2007). Adverse late effects of childhood cancer and its treatment on health and performance. *Annual Review of Public Health, 28*, 279 302.

Panigrahy, A., & Bluml, S. (2009). Neuroimaging of pediatric brain tumors: From basic to advanced magnetic resonance imaging (MRI). *Journal of Child Neurology, 24*, 1343-1365.

Robinson, K. E., Kuttesch, J. F., Champion, J. E., Andreotti, C. F., Hipp, D. W., Bettis,

A., … Compas, B. E. (2010). A quantitative meta-analysis of neurocognitive sequelae in survivors of pediatric brain tumors. *Pediatric Blood and Cancer, 55*, 525-531.

Robinson, K. E., Livesay, K. L., Campbell, L. K., Scaduto, M., Cannistraci, C. J., Anderson, A. W., … Compas, B. E. (2010). Working memory in survivors of acute lymphocytic leukemia: Functional neuroimaging analyses. *Pediatric Blood and Cancer, 54*, 585-590.

Schultz, K. A., Ness, K. K., Whitton, J., Recklitis, C., Zebrack, B., Robison, L. L., … Mertens, A. C. (2007). Behavioral and social outcomes in adolescent survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Journal of Clinical Oncology, 25*, 3649-3656.

Spadoni, A. D., Bazinet, A. D., Fryer, S. L., Tapert, S. F., Mattson, S. N., & Riley, E. P. (2009). BOLD response during spatial working memory in youth with heavy prenatal alcohol exposure. *Alcoholism: Clinical and Experimental Research, 33*, 2067-2076.

Spiegler, Brenda J., Eric Bouffet, Mark L. Greenberg, James T. Rutka and Donald J. Mabbott (2004). Change in neurocognitive functioning after treatment with cranial radiation in childhood. Journal of Clinical Oncology, 22, 706-713.

Stargatt, R., Rosenfeld, J. V., Maixner, W., & Ashley, D. (2007). Multiple factors ontribute to neuropsychological outcome in children with posterior fossa tumors. *Developmental Neuropsychology, 32*, 729-748.

Sweet, L. H., Rao, S. M., Primeau, M., Durgerian, S., & Cohen, R. A. (2006). Functional magnetic resonance imaging response to increased verbal working memory

demands among patients with multiple sclerosis. *Human Brain Mapping, 27*, 28-36.

Vogt, B. and A. Peters (2004). Form and distribution of neurons in rat cingulate cortex: Areas 32, 24, and 29. *The Journal of Comparative Anatomy, 19,* 603-625.

Wechsler, D. (2003). *Wechsler Intelligence Scale for Children – Fourth Edition Technical and Interpretive Manual.* San Antonio, TX: The Psychological Corporation.

Zebrack, B. J., & Chesler, M. (2001). Health-related worries, self image, and life outlooks of long term survivors of childhood cancer. *Health and Social Work, 26*, 245-256.

Table 1
Demographics of BT Survivors and Healthy Controls

Variables	**BT**	**Healthy Control**	**χ^2 (p)**
Sex			
Female	12 (60%)	9 (45%)	.90 (.34)
Male	8 (40%)	11 (55%)	
Race/ethnicity (n, %)			
White/Caucasian	18 (90%)	12 (60%)	5.77 (.12)
Black/African American	1 (5%)	6 (30%)	
Latino	0	1 (5%)	
Asian/ Pacific Islander	1 (5%)	1 (5%)	
Primary Caregiver (n, %)			
Mother	17 (85%)	20 (100%)	3.24 (.072)
Father	3 (15%)	0	
Parent Education (n, %)			
≤ High School Graduation	4 (20%)	0	4.44 (.04)*
> High School Graduation	16 (80.%)	20 (100%)	
Household Income			
<$50,000/year	8 (40%)	9 (45%)	1.06 (.59)
≥$50,000/year	11 (55%)	11 (55%)	
Rather Not Say	1 (5%)	0	
Age at Enrollment (in years)			
Mean (SD)	12.15 (2.72)	12 (2.98)	5.69 (.68)
Range	8.00 – 16.00	8.00 – 16.00	

T-statistic reported for Age at Assessment. Chi-squares are reported for all other variables.
*p≤.05, **p≤.01, ***p≤.001

Table 2
Descriptive Statistics: BRIEF, WISC, RSQ, YSR, CBCL, BOLD

Overall Cognitive Ability and Executive Function	**BT Group Mean (SD)**	**HC Group Mean (SD)**	**t (p)**
BRIEF Working Memory Scale	61.60 (12.91)	53.15 (11.60)	2.177 (.04)*
WISC-IV WMI Composite Score	90.10 (12.33)	101.05 (12.44)	-2.80 (.01)**
RSQ Scales			
Primary Control Engagement	.17 (.06)	.20 (.06)	-1.81 (.08)
Secondary Control Engagement	.28 (.17)	.26 (.07)	.59 (.56)
Disengagement	.14 (.05)	.16 (.02)	-.99 (.33)
Emotional/Behavioral Outcomes			
YSR Anxious/Depressed	57.63 (10.31)	54.32 (4.42)	1.29 (.21)
CBCL Anxious/Depressed	58.9 (8.01)	55.35 (9.63)	1.27 (.21)
YSR Withdrawn/Depressed	58.63 (8.71)	55.05 (5.45)	1.52 (.14)
CBCL Withdrawn/Depressed	60.50 (8.00)	54.00 (5.13)	3.06 (.00)**
N-Back Variables			
3v0-Back: Cluster 19 – BA 32	.02 (.22)	.21 (.18)	-2.71 (.01)**
0-Back Accuracy	43.56 (2.73)	44.47 (1.94)	-1.11 (.26)
1-Back Accuracy	43.33 (2.83)	44.59 (1.46)	-1.63 (.11)
2-Back Accuracy	41.50 (2.55)	42.35 (3.02)	-.91 (.37)
3-Back Accuracy	37.50 (2.60)	40.41 (2.37)	-3.46 (.00)**

Note: T Scores were used in these analyses; Higher scores on the BRIEF indicate poorer performance
*p≤.05, **p≤.01, ***p≤.001

Table 3

Correlations of Group, BRIEF, WISC, RSQ, YSR, CBCL, and BOLD Activation

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
1. BT or HC	--										
2. BRIEF WM Scale	**-.33***	--									
3. WISC WMI Composite	**.41****	**-.44****	--								
4. RSQ – Primary Control	.28	-.03	**.41****	--							
5. RSQ – Secondary Control	-.10	.17	**-.33***	-.24	--						
6. RSQ - Disengagement	.16	**-.41****	**.38***	.29	**-.34***	--					
7. YSR Anxious/Depressed	-.21	.03	-.14	**-.27**	**-.37***	**.40***	--				
8. CBCL Anxious/Depressed	-.20	.28	-.26	-.15	.12	.02	.24	--			
9. YSR Withdrawn/Depressed	-.25	.05	.05	-.28	-.28	**.34***	**.74***	.047	--		
10. CBCL Withdrawn/Depressed	**-.45****	-.40*	-.26	-.09	.28	-.07	.13	**.60****	.18	--	
11. 3v0 Back Cluster 19 – BA 32	**.44***	-.28	.20	.08	-.05	-.07	.07	-.24	.29	-.26	--

Note: BRIEF scales were reverse scored such that lower scores rather than higher scores indicate poorer functioning
*p≤.05, **p≤.01, ***p≤.001

Table 4

Regression Equation Testing Factors of CBCL Withdrawn/Depressive Symptoms as Dependent Variable

Step	Predictors	β	t(p)	R^2	R^2 Change	F-Change
Step 1: WISC-IV WMI	WMI	-.50	-3.16**	.25	.25	10.00
Step 2: Group	WMI	-.32	-1.93	.37	.122	5.65
	Group	-.39	-2.38*			
Step 3: RSQ Secondary Control	WMI	-.25	-1.41	.40	.03	1.25
	Group	-.37	-2.35*			
	RSQ Secondary	.18	1.12			
Step 4: 3v0-back BA 32 BOLD	WMI	-.25	-1.38	.40	.00	.05
	Group	-.37	-2.03			
	RSQ Secondary	.18	1.12			
	3v0 BOLD	-.04	-.22			

*p≤.05, **p≤.01, ***p≤.001

Table 5

Regression Equation Testing Factors of Secondary Control Coping as Dependent Variable

Step	Predictors	β	t(p)	R^2	R^2 - Change	F-Change
Step 1: WISC-IV WMI	WMI	-.004	-2.44*	.17	.17	5.95
Step 2: Group	WMI	-.004	-2.055*	.17	.001	.03
	Group	-.008	-.17			
Step 3: CBCL Withdrawn/Depressed	WMI	-.003	.911	.20	.04	1.25
	Group	.02	-1.57			
	CBCL W/D	.004	.30			
Step 4: 3v0-back BA 32 BOLD	WMI	-.003	.91	.21	.004	.12
	Group	.009	-1.54			
	CBCL W/D	.004	.15			
	3v0 BOLD	.039	1.12			

*p≤.05, **p≤.01, ***p≤.001

Table 6.

Regression Equation Testing 3v0 BOLD activation for BA 32 as Dependent Variable

Step	Predictors	β	t(p)	R^2	R^2 - Change	F-Change
Step 1: WISC-IV WMI	WMI	-.004	-2.44*	.17	.17	5.95
Step 2: Group	WMI	-.004	-2.055*	.17	.001	.03
	Group	-.008	-.17			
Step 3: Secondary Control Coping	WMI	-.003	.911	.20	.04	1.25
	Group	.02	-1.57			
	RSQ Secondary	.004	.30			
Step 4: CBCL Withdrawn/Depressed	WMI	-.003	.91	.21	.004	.12
	Group	.009	-1.54			
	RSQ Secondary	.004	.15			
	CBCL W/D	.039	1.12			

*p≤.05, **p≤.01, ***p≤.001